REMARKS

The Rejections Under 35 USC § 112

Applicants respectfully disagree with the rejection regarding the hydrates and salts thereof; nevertheless, to advance the application to an expeditious allowance, these terms have been cancelled from the claims, rendering this rejection moot.

The Office Action alleges that the application does not enable substituents other than H, alkyl, alkoxycarbonylalkyl and cyano.

Applicants respectfully traverse this rejection, as it is clearly improper especially in view of even specific species taught in the application having other substituents than those admittedly enabled. See, for example, the compounds of the examples, having various substituents, e.g., hydroxyl, alkoxy, carboxylic acid alkyl ester or amide, halogen, substituted aryl with various substituents, alkylamino, fluorinated alkoxy, nitro, heteroaryl, etc. See, the examples. Moreover, the application teaches the compounds can be prepared by art-known matter, as disclosed in a large number of cited references. See, e.g., the bottom of page 63 citing to various WO publications. General reaction schemes are also taught beginning on page 64, including teaching on how to prepare various intermediates, while indicating that many intermediate compounds are commercially available in the middle of page 65, for example.

In view of the vast and detailed amount of teaching in the application in view of what is known in the art, applicants submit that there is no basis for the rejection of the claimed compounds for the lack of enablement.

The Office Action appears to treat the compound claims as if they were method claims directed to a variety of specific uses, i.e., a pharmaceutical applications requiring *in vivo* and *in vitro* screening. However, here a compound is claimed, therefore a compound is what needs to be enabled. The compound claims are not limited to a specified use as a method claim may be. The compound may be used for any purpose, including, e.g., the *in vitro* aspects taught in the specification or *in vivo* ones and others.

The Federal Circuit has specifically held that a composition claim can not be read to embrace only certain uses because the composition claims would otherwise mutate into a method claim. See *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000), wherein the Federal Circuit stated that "the '393 patent **claims compositions of matter. The scope of these composition claims cannot ... embrace**

only certain uses of that composition. ... Otherwise these composition claims would mutate into method claims."

Also important to note is the analysis used by the Federal Circuit in determining whether a pharmaceutical composition was enabled in *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003). The inquiry exclusively focused on whether the individual components of a pharmaceutical composition were enabled and not on whether a particular use of said composition would be enabled. See the relevant part of the *Amgen* decision, which is reproduced below.

> Focusing specifically on the '422 patent, **the enablement inquiry** is whether Amgen has enabled all **pharmaceutical compositions** comprising "a therapeutically effective amount of human erythropoietin," "a pharmaceutically acceptable diluent, adjuvant or carrier," and human erythropoietin "purified from mammalian cells grown in culture." The court found that the specification described and enabled various possible diluents and carriers and provided specific information on effective dosages and therapeutic effect in mice. Id. at 148, 57 USPQ2d at 1506. Amgen also described and enabled at least one way of obtaining EPO purified from mammalian cells in culture: the genetic manipulation of CHO and COS-1 cells, followed by both described and other well known purification techniques. Finally, the court accepted testimony indicating that an ordinarily skilled artisan would infer from the COS-1 (monkey) and CHO cell examples that similar outcomes could be expected from other mammalian cells since all mammalian cells produce and secrete hormones like EPO by means of the same fundamental processes. Id. at 159, 57 USPQ2d at 1514-15. (Emphasis added.)

There is no basis for treating compound claims as if they were method claims directed to particular uses.

Additionally, even if the enablement of compound claims would require *in vitro* and *in vivo* screening, there is no basis for the rejection. The requirement of screening is not undue experimentation in the field of pharmaceuticals, but rather an industry wide acceptable routine amount of testing. As discussed in *Wands* cited by the Office Action, the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

The Office Action also alleges that the "pharmaceutical art is unpredictable," citing *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) in support. However, there is no basis for such an allegation or conclusion. Fisher does not stand for the proposition that the pharmaceutical art is unpredictable *per se*. The court in *Fisher* stated that "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." Thus, merely concluding that the pharmaceutical art is unpredictable without looking at the factors involved is an improper basis for the allegation. As discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), used by the Examiner as the basis of the rejections, the court therein teaches that "whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." No factual basis is provided by the Office Action for the conclusion that the relevant art is unpredictable.

Additionally, with respect to *Fisher*, the court held therein that the appellant, who was the first to achieve a potency of greater than 1.0 for adrenocorticotrophic hormones ("ACTHs"), had not enabled the preparation of ACTHs having potencies much greater than 2.3, and the claim recitations of potency of "at least 1" rendered the claims insufficiently supported under the first paragraph of 35 U.S.C. §112. Thus, the situation and question considered by the court in *Fisher* is very different than the one present case. The applicant therein was the "first" to achieve a potency of greater than 1.0, but not greater than 2.3, while the claims were directed with an open end to a potency of "at least 1." In the present case, other compounds are already known to treat conditions claimed, and the claims are not open ended.

The Office Action also cites to a reference teaching that „most non-chemists would probably be horrified if they were to learn how many attempted synthesis fail, ..." Said citation is however completely irrelevant here. The target audience of a patent or patent application related to chemistry is not „non-chemists," but those of ordinary skill in the art.

The Office Action also alleges that the specification does not have any working example; yet the Office Action immediately thereafter admits that the specification provides some data on page 85 related to antiproliferative activity. Thus, the allegation that there are no working examples is incorrect. Biological investigations are described starting from page 85 of the application with results provided for 16 compounds of the application.

Additionally, examples directed to the preparation of a large number of species are provided on pages 68 to 75.

Moreover, there is no requirement for any examples or data in an application. See, for example, *Marzocchi*, supra, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." (Emphasis added.) The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." (Emphasis added.) See MPEP § 2164.02.

For all the foregoing, reconsideration is respectfully requested.

The Rejections Under 35 USC § 103

Applicants respectfully disagree with the rejections, but to advance the application to an expeditious allowance, amended the claims to even further distinguish them from the compounds of the cited references (WO '877, WO '117 and 'WO '116).

The definition of R41 is limited to 1-4C-alkyl. Such a substituent is not even generically disclosed by the cited references. Said R41 group along with the already identified differences by the Examiner sufficiently patentably distinguishes the claimed invention of the present application from the disclosures of the references.

Nevertheless, applicants provide the following comments.

The Office Action appears to take the substituents form various species and combine them and view them in view of the generic disclosure. However, under well-settled patent law, such an approach is inappropriate.

Note in this regard, particularly, the analysis used by the Court in *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992). The group at issue in Jones had the structure

$$-NH_2-CH_2CH_2-O-CH_2CH_2OH.$$

The PTO tried to rely on the single reference's compound having two CH_2CH_2OH groups attached to a single N atom, instead of linked together as shown above. The Court stated that one could not ignore the fact that the two CH_2CH_2OH groups were not joined together to form the ether linkage-containing group required in the claim. One could not simply rely on the "$-CH_2CH_2O-$" features of the reference; one had to consider the entirety of the structure involved. The Patent and Trademark Office also tried to rely on a morpholino group in the single reference wherein the nitrogen atom has two ethyl groups bonded to it and linked to

each other by a single oxygen atom, thereby allegedly providing the "missing" ether oxygen noted above. Again, the Court stated that one could not ignore the entirety of the structure, i.e., the fact that this prior art group compound was cyclic. One could not apply components of its structural features in isolation apart from the group's overall structure. Other similar analyses were rejected by the Court.

Likewise here to the situation in *Jones*, the disclosed species have different substituents on the phenyl group in the position of R5 of the cited references. No reason is provided to one of ordinary skill in the art to, e.g., remove a halogen group or carboxylic acid group and then to replace them with a different, e.g., alkyl, substituent. Moreover, in view of *Jones*, it is improper to piece together the individual species with each other or with the general disclosure.

Additionally, with the current amendment, in addition to the modifications allegedly obvious (which is not admitted), one of ordinary skill in the art would have to also modify the compounds of the cited references at the corresponding position to R41 of the present claims, for which also no motivation is present in any of the cited references. Given the multiplicity of modifications required to any given disclosed compound in the cited art, the rejections cannot be maintained.

More recent decisions of the Federal Circuit approached the issue of structural obviousness as set forth in, e.g., *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. et al.*, 87 USPQ2d 1452 (Fed. Cir. 2008).

One of the issues in *Takeda* was whether picking a specific compound as a starting point (lead compound) from the prior art disclosing it and several others is obvious without a reason leading to its choice. The Federal Circuit's answer was no.

The prior art reference in *Takeda* taught the exact same use for the compounds as claimed in the later application (antidiabetic treatment), taught 34 compounds specifically from a broad generically disclosed formula, including the specific compound of interest in the later application, the prosecution history of the prior art reference supplied test data for nine specific compounds, including the specific compound of interest, the compound of interest was specifically claimed in one of the patents in the prior art patent family, i.e., a claim specifically was directed to the compound of interest alone (see claim 4 of US 4,444,779),

and the prosecution history thereof included a statement to the effect that the claimed compounds became important, especially the compound of interest.

A separate prior art document tested 101 various prior art compounds, including the compound of interest, and indicated some side effects associated with the compound of interest.

The lower court held, which holding was upheld by the Federal Circuit, that the selection of the compound of interest as a lead compound was not obvious in view of the prior art. The lower court held that any "suggestion to select" the compound of interest was negated by the separate prior art document testing various prior art compounds. (Emphasis added.) The Federal Circuit rejected arguments relying on *KSR* that "the claimed compounds would have been obvious because the prior art compound fell within 'the objective reach of the claims.'"

Thus, it is clear that the law requires "suggestion to select" the compounds of interest from the prior art, and it is not adequate that a compound merely fall within the objective reach of a claim.

The Federal Circuit in *Eisai* characterized the holding of Takeda by stating that "obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound." Emphasis added.

The court went on to summarize the state of the law of obviousness, especially as it pertains to chemical arts, as follows:

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might **identify a problem and pursue potential solutions**. Second, KSR presupposes that the record up to the time of invention would **give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound**. See Takeda, 492, F.3d at 1357 ("Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness*** of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would **supply some reasons for narrowing the**

> **prior art universe to a "finite number of identified, predictable solutions,"** 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that **this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable**. (Emphasis added.)

The compound of the claims in *Eisai*, i.e., Lansoprazole, was in an art where the core of the compound was known and described in a class of compounds by a reference, i.e., Brändström. Rabeprazole, a specific prior art compound, had the same core and substituents thereon with the exception of an $OCH_2CH_2CH_2OCH_3$ group in the 4-position, where the claimed Lansoprazole has an OCH_2CF_3 group. Omeprazole, another compound sharing the same core has an OCH_3 group in the 4-position. The Federal Circuit even taking the evidence most favorable to the movant on Summary Judgment challenging the validity of the patent did not find obviousness. There was evidence in the record that the fluorinated substituent on the lead, i.e., Lansoprazole, which was selected as the allegedly obvious lead by the movant, provided a special path to achieving lipophilicity. Without discernible reason on the record why one of ordinary skill in the art would have modified this group, which was known to provide lipophilicity, the Federal Circuit held that there was no obviousness.

In the present case the cited references teach a very large number of compounds, i.e., WO '877 teaches 438 specific compounds, WO '116 teaches 92 compounds and WO '117 teaches 29 compounds. No reason is identified by the Office Action why one of ordinary skill in the art would have selected the specific compounds identified in the Office Action as a lead compound available for various modifications. With such a shortcoming in establishing obviousness, the rejections should be withdrawn. Additionally, no reason is provided for the modifications necessary to achieve the presently claimed invention, e.g., the removal of an OH group, or halogen group, etc., and the additional of a group corresponding to applicant's R41 group, for which not even a generic teaching is provided in the prior art. One of ordinary skill in the art would not have been able to predict the result of said multiple modifications on the activity of the compounds. As such, the modifications required were not a finite number of identified, predictable solutions.

Reconsideration is respectfully and courteously requested.

Double Patenting

The Office Action rejects claims 1 and 21 under statutory double patenting over claims 1 and 17 of co-pending US 10/562,137. Because the scopes of these claims are not identical, this rejection is improper. Accordingly, the withdrawal thereof is respectfully solicited. Additionally note that the assignees of these applications are also not the same.

The compounds of the present claims differ in the definition of R8 from the R8 groups in the claims of US '494 and also of US '497. R8 in the present claims is phenyl, phenylcarbonyl, -C(O)-N(R82)R83 or -C(O)-OR9, while in US '494 it is C(O)-R9 and in US '497 it is a Het4 group optionally substituted by R81, wehre Het4 isoxadiazolyl or oxazolyl group. The claims of these applications do not render the claims of the present application obvious.

Moreover, the provisional obviousness-type double patenting rejections over US '494 and '497 should be withdrawn also for being in later filed pending applications. MPEP 804(I)(B)(1) states that

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Accordingly, the withdrawal of these rejections is respectfully requested upon the resolution of the other rejections herein in case not already considered moot in view on the merits.

Withdrawn Claims

A bring the attention of the Examiner to MPEP § 821.04, Rejoinder, which states that "if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims [both process of making and using] which either depend from or include all the limitations of the allowable product will be rejoined."

The present method claims depend from the elected product claims.

Accordingly, upon allowance of the elected product claims, the rejoinder of the non-elected claims is respectfully requested in accord with the rejoinder provisions of the MPEP.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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